LETTERS

Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disorder of unknown aetiology that leads to death in the majority of patients within 3–5 years of diagnosis. One of the most prominent features of IPF is a disabling and resistant to traditional anti-inflammatory treatment cough. The mechanism by which thalidomide suppresses the cough is unknown, but we hypothesise that it is due either to anti-inflammatory properties or a direct inhibitory effect on pulmonary sensory nerve fibres. As chronic cough has been associated with significant deterioration in patient’s quality of life, amelioration of the IPF cough with thalidomide may be beneficial for these patients with an incurable progressive disease.

In summary, our observations suggest that future clinical trials using low dose thalidomide for the suppression of cough in IPF are warranted.

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REFERENCES


Counting, analysing and reporting exacerbations of COPD in randomised controlled trials

I read with interest the article by Aaron et al. In this paper, data from the Optimal Trial were reanalysed for the purpose of examining the effect of differences in counting and analysing exacerbation rates on estimated treatment effects in chronic obstructive pulmonary disease (COPD). The authors compare exacerbation rates in two of the three treatment arms in the trial (i.e., those randomly allocated to tiotropium + placebo or to tiotropium + fluticasone–salmeterol). They compare an “intention to treat” strategy with a strategy using “time in study only” and state that the often used method of excluding patients after they stop study medication exaggerates the estimated benefits of treatment.

Data from large controlled trials are often reanalysed and they usually provide a good and solid database for assessment of methodology. However, when trials are reused, the original study is often only described briefly in secondary publications and often crucial information is missing. This seems to be the case for the reanalysis of the Optimal Study. In the original report, the numbers of patients withdrawing from the tiotropium + placebo group and the tiotropium + fluticasone–salmeterol group within the 52 week treatment period were 74 (47%) and 37 (26%), respectively, indicating less treatment efficacy in the former group. In the original paper—but not in the reanalysis—it is also shown that of the patients who discontinued use of study medications, 74% in the tiotropium + placebo group and 54% in the tiotropium + fluticasone–salmeterol group received an open label inhaled steroid and long acting beta2 agonist combination inhaler for the remainder of the study. That approximately half of the patients randomised to tiotropium + fluticasone–salmeterol were given the same type of treatment does not substantially affect the analyses. However, when those stopping tiotropium + placebo are given an open label inhaled steroid and long acting beta2 agonist combination inhaler for the remainder of the study it is not surprising that the “intention to treat strategy” dilutes the effect of the triple combination treatment. Although we all want conservative treatment estimates from controlled trials, there is a real risk of getting not just conservative but in fact insignificant findings if the actual study...
comparison differs significantly from the setting described in the study protocol. Aaron et al advocate that any intention to treat analysis is superior to other strategies. However, when withdrawal rates are substantial, as in the Optimal Trial, and patients withdrawing from study medication are given medication being tested in the trial, any conclusion on analysis methodology should be made with caution.

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Competing interests: JV has been involved in clinical trials of inhaled corticosteroid alone or in combination with long acting beta agonists; his wife is an employee of AstraZeneca.

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Author’s reply
We would like to thank Dr Vestbo for his comments. We agree that in the Optimal Trial more patients originally randomised to the placebo arm prematurely discontinued study medications, and that many of these patients were subsequently put on open label ICS/LABA products.1 As discussed in our paper, the relative risk reduction decreased from 21% if patients were prematurely excluded once they discontinued study drugs to 15% when an intent to treat analysis was used.2 We agree with Dr Vestbo that our intention to treat analysis was conservative, and it did slightly reduce the possibility of a difference being found between placebo and active treatment but we would argue that this analysis was necessary in order to prevent bias.

An intention to treat analysis is necessary as it is impossible to know a priori the ultimate direction of the bias when patients who stop study medications early are banished from a clinical trial. Will the bias favour the drug or favour placebo? For example, a similar analysis of a trial assessing tiotropium for chronic obstructive pulmonary disease (COPD)1 showed that the bias can work exactly in the opposite direction and instead favour placebo over active drug. In this study, higher incidence rates of fatal events occurred following premature discontinuation of study medication, especially in those patients randomised to the placebo arm. Presumably, patients who were taking placebo in this study were doing poorly and many prematurely stopped study drugs and then, shortly thereafter, they died. In this case, early exclusion of these patients would have introduced bias because the factors which determined whether a patient might have been included were also related to the outcome. If these patients had been dropped from the trial after premature discontinuation of study medications, this would have meant that their deaths would not have been discovered, and this would have produced a biased mortality incidence ratio in favour of placebo over tiotropium. The authors of this study concluded that failure to consider outcomes of patients who discontinue study medications early may bias results against effective therapies.3 Only by ensuring full follow-up of all randomised patients and by using a proper intention to treat analysis was this potential bias eliminated.

There is an old saying in medicine “You can’t find a fever if you don’t take a temperature”. This applies to clinical trials as well; the investigator cannot know what really happened in a clinical trial unless he/she evaluates outcomes in all randomised patients for the full study follow-up period, regardless of patient compliance.

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IL1 may be elevated but is it all bad in ARDS?

Frank et al have elegantly demonstrated in animal models of ventilator associated lung injury (VALI) that interleukin 1β (IL1β) may play a role in the development of alveolar barrier dysfunction. However, the ventilation strategy used for these experiments (with a very high tidal volume of 30 ml/kg) induced an increase in IL1β of only 36 pg/ml in lavage as opposed to 7 pg/ml in their control animals, a level that in their in vitro models of epithelial resistance and permeability did not significantly affect permeability.1

Our recent study published in Thorax has evaluated IL1β levels in bronchoalveolar lavage fluid in patients with adult respiratory distress syndrome (ARDS) as 145 pg/ml.2 Thus their animal model does not adequately reflect the in vivo situation in patients with established ARDS. We believe this may be important because several lines of evidence suggest that IL1β may play a role in stimulating repair of the alveolar epithelium.

Effective alveolar repair following the development of ARDS is believed to involve the transdifferentiation of alveolar type II cells (ATII), which retain stem cell-like properties, into type I cells via intermediate cell phenotypes. The turnover rate of ATII cells is boosted after acute lung injury and the recovery process is believed to involve cell migration and proliferation in addition to transdifferentiation of ATII epithelial cells.3 4 Geiser et al were the first to show that pulmonary oedema fluid, early in the course of ARDS, stimulates repair of wounded monolayers in culture to a greater extent than plasma obtained from the same patients or pulmonary oedema fluid from patients with hydrostatic oedema.5 The potential of oedema fluid to promote wound repair was associated with a trend towards improved survival and reduction in the duration of ventilation. The enhanced wound repair is IL1β dependent and mediated by autocrine release of epidermal growth factor and transforming growth factor α.6 Recently, we have further demonstrated that lung lavage fluid from ARDS patients treated with intravenous salbutamol enhanced A549 monolayer wound repair responses compared with placebo treated patients in vitro by an IL1β dependent mechanism.7

In conclusion, the data from the study by Frank et al clearly demonstrate that increased IL1 signalling may be an early mechanism of alveolar barrier dysfunction in VALI in rats and mice. However, significant evidence suggests that once ARDS is established, elevated IL1 levels may have beneficial effects on epithelial repair. We believe that this may therefore account for the apparent failure of anti-IL1 strategies in humans with ARDS.

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